

Appl. No. 09/700,712  
Amendment dated: January 16, 2007  
Reply to OA of: September 13, 2006

### **REMARKS**

This is in response to the Official Action of September 13, 2006 in connection with the above-identified application. Applicants have amended the claims of the instant application in order to more precisely define the scope of the present invention, taking into consideration the outstanding Official Action. The amendments to the claims made herein will be discussed while addressing the objections and rejections set forth in the outstanding Official Action.

To begin with, Applicants acknowledge sections 1-6 and 8-15 in the outstanding Official Action. Applicants respectfully submit that no response to these paragraphs is necessary.

With respect to section 7 of the outstanding Official Action, the Official Action urges that the objection to claims 23 as set forth in section 20(b) of the Official Action dated July 7, 2005 is maintained. Section 20(b) of the Official Action dated July 7, 2005 suggests that claim 23 be amended to recite "the *thyA* gene in the chromosome has the nucleotide sequence of SEQ ID NO: 1" for the sake of clarity. Accordingly, Applicants have amended claim 23 according to the suggestion set forth in the Official Action dated July 7, 2005. In light of this amendment, Applicants respectfully request that the objection to claim 23 be withdrawn.

With respect to section 16 of the outstanding Official Action, the Official Action urges that claim 17, and claims 19-23 and 26-29 that depend therefrom, are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the outstanding Official Action alleges that the recitation in claim 17 of "by selected nucleotide sequence deletion and/or insertion in the chromosome" constitutes the addition of new matter to the application.

Applicants note the final paragraph of section 16 wherein it is stated that this rejection may be overcome by removing the new matter from the claim. Accordingly, Applicants have deleted the phrase "by selected nucleotide sequence deletion and/or insertion in the chromosome" from claim 17. In light of this amendment, Applicants

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respectfully submit that the §112, first paragraph, rejection of claims 17, 19-23 and 26-29 as set forth in section 16 of the outstanding Official Action has been rendered moot and should therefore be withdrawn.

With respect to section 17 of the outstanding Official Action, the Official Action urges that claim 24 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the outstanding Official Action alleges that the recitation in claim 24 of “*DthyA* strain of *Vibrio cholerae*”, “structural *thyA* gene of the chromosome having the nucleotide sequence of nucleotides 738-1688 in the SEQ ID NO:1”, “approximately 200 base pairs” and “structural *thyA* gene is deleted followed by an insert of a non-coding region of DNA” each constitute the addition of new matter to the application.

Beginning with the recitation of “*DthyA* strain of *Vibrio cholerae*” in claim 24, Applicants respectfully submit that this represents a typographical error in the claims. Specifically, in preparing the previous response, the D was not properly formatted to read as a  $\Delta$ . Accordingly, Applicants have amended claim 24 to recite “ $\Delta$  *thyA*” in place of “*DthyA*”.

Claim 24 has also been amended to delete the recitation of a “structural *thyA* gene” to address the new matter rejection. In light of this amendment, claim 24 now recites a “*thyA* gene”, which is clearly supported by the specification as originally filed.

Finally, with respect to the recitation of the phrases “approximately 200 base pairs” and “structural *thyA* gene is deleted followed by an insert of a non-coding region of DNA”, Applicants note that these phrases have been replaced with the phrase “wherein 209 basepairs from said *thyA* gene have been deleted and 261 basepairs from Kan<sup>R</sup> geneblock have been removed”. The paragraph bridging page 10 and 11 in the originally filed specification states that a nonreversible *thyA* mutation was obtained by deleting 209 basepairs from the *thyA* gene and removal of 261 basepairs from the Kan<sup>R</sup> geneblock. Furthermore, the primers appear on page 11, lines 7-11 of the originally filed specification, and provide the exact position of the deletion. One of ordinary skill

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in the art can see from the primers within the frame on page 11 and Figure 11 of the instant application that the *thyA* gene in the chromosome has the nucleotide sequence of nucleotides 738-1688 in the SEQ ID NO: 1. Accordingly, Applicants respectfully submit that the alleged new matter has been removed from claim 24 and replaced with subject matter that is clearly supported by the specification as originally filed.

In light of these amendments to claim 24, Applicants respectfully request that the §112, first paragraph, rejection of claim 24 as set forth in section 17 of the outstanding Official Action be withdrawn.

With respect to section 18 of the outstanding Official Action, the Official Action urges that claims 25 and 26, and those depending therefrom, are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the outstanding Official Action alleges that the recitation in claims 25 and 26 of “wherein the strain has its structural *thyA* gene removed from the *thyA* gene of the chromosome” constitutes the addition of new matter to the application.”

Applicants note that claims 25 and 26 have been amended to delete the word “structural” and also to recite “wherein the strain has its *thyA* gene removed from the *thyA* gene locus in the chromosome”. At page 3, lines 9 and 10 of the instant application it is stated that site-directed mutagenesis in the *V. cholerae* chromosome for the deletion and/or insertion of gene nucleotides is at the locus of *thyA* gene having essentially the nucleotide sequences SEQ ID NO: 1. Therefore, Applicants respectfully submit that the amended claims are supported by the specification as originally filed.

In light of the amendments to claims 25 and 26 replacing the alleged new matter with subject matter that is supported by the specification as originally filed, Applicants respectfully request that the §112, first paragraph, rejection of claims 25 and 26 as set forth in section 18 of the outstanding Official Action be withdrawn.

With respect to section 19 of the outstanding Official Action, the Official Action urges that claims 17-29 are rejected under 35 U.S.C. §112, first paragraph, as failing

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to provide an adequate written description of the invention and for failing to provide an enabling disclosure. Specifically, the Official Action alleges that the specification does not provide evidence that the claimed biological material is (1) known and readily available to the public; (2) reproducible from the written description, e.g., sequenced; or (3) deposited.

Applicants respectfully traverse this rejection because the claimed biological material is reproducible from the written description. Applicants draw attention to page 7, line 15 of the instant application, wherein it is stated that the *thyA* gene was cloned from strain *V. cholerae* JS1569, which strain originates from the *V. cholerae* Inaba strain 569B of the classical biotype (ATCC No. 25870). The strain has a deletion in the *ctxA* gene (see, e.g., Kaper, J.B., H. Lockman, M. M. Baldini, and M. M. Levine. 1984. A recombinant live oral cholera vaccine. *Biotechnology* 2:345-349) and has been made rifampicin resistant (see, e.g., Sanchez, J., and J. Holmgren. 1989. Recombinant system for overexpression of cholera toxin B subunit in *Vibrio chlorerae* as a basis for vaccine development. *Proc. Natl. Acad. Sci. USA*. 86:481-485). Thus, the strain *V. chlorerae* JS1569 is fully described by the ATCC number and the references cited. Starting from the last mentioned strain, all the necessary steps to obtain the claimed  $\Delta$  *thyA* strain appear in the specification with the aid of drawings and the primers disclosed. The strain has therefore not been deposited since it is fully reproducible by one of ordinary skill in the art from the disclosure in the specification and the drawings discussed above.

In light of the above comments, Applicants respectfully request that the rejection of claims 17-29 under 35 U.S.C. §112, first paragraph, as set forth in section 19 of the outstanding Official Action be withdrawn.

With respect to section 20 of the outstanding Official Action, the Official Action urges that claims 17-29 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants have amended the claims in order to overcome the rejection set forth in section 20 as described below.

With respect to section 20(a), Applicants note that, as discussed above, claim 24 has been amended to recite " $\Delta$  *thyA*" in place of "*DthyA*".

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With respect to section 20(b), Applicants note that, as discussed above, claim 24 has been amended to delete the word "structural".

With respect to sections 20(c) and 20(d), Applicants note that, as discussed above, claims 25 and 26 have been amended to delete the word "structural" and to recite "wherein the strain has its *thyA* gene removed from the *thyA* gene locus in the chromosome".

With respect to section 20(e), Applicants note that, as discussed above, claim 24 has been amended to delete the phrases "approximately 200 base pairs" and "insert of a non-coding region of DNA".

With respect to section 20(f), Applicants note that, in order to address the issue of antecedent basis raised in the Official Action, claim 17 has been amended to recite "the at least one episomal autonomously replicating DNA element further comprises" as suggested in the Official Action

With respect to section 20(g), Applicants note that claim 18 has been amended such that the word *cholerae* is italicized.

With respect to section 20(h), Applicants note that claim 20 has been amended to recite "wherein the at least one episomal autonomously replicating DNA element has".

With respect to section 20(i), Applicants note that claim 24 has been amended such that "*thyA* gene" is used consistently throughout the claim.

With respect to section 20(j), Applicants respectfully submit that in light of the above amendments to claims 17 and 18, any issues of indefiniteness in claims 19-29 have been resolved.

In light of the above amendments to claims 17, 18, 20 and 24-26, Applicants respectfully submit that all claims now pending in the instant application are in compliance with 35 U.S.C. §112, second paragraph, and therefore the rejections set forth in section 20(a)-(j) should be withdrawn.

With respect to section 21 of the outstanding Official Action, the Official Action urges that claims 17-19 are rejected under 35 U.S.C. §102(b) as being anticipated by Valle *et al.* (*Infect. Immun.* 68: 6411-6418, Nov 2000). Applicants respectfully traverse

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this rejection because the Valle reference does not qualify as prior art under 35 U.S.C. §102(b).

As acknowledged at section 6 of the Official Action dated September 23, 2004, "the instant application is a national stage 371 application of PCT/EP99/03509, filed May 21, 1999 and claims foreign priority to the application, 9801852-6, filed May 26, 1998". Thus, the instant application has a priority date that is prior to the publication date of the Valle reference. Accordingly, Applicants respectfully submit that the Valle reference does not qualify as prior art under 35 U.S.C. §102(b), and the rejection set forth in section 21 of the outstanding Official Action should therefore be withdrawn.

Applicants also note the assertion in the Official Action that the Valle reference has a publication date of November 1, 2000. This publication date appears to be unsubstantiated. Specifically, Applicants note that the reference supplied with the outstanding Official Action lists a publication date of November 2000 in the upper left hand corner, but provides no evidence that the publication was available on November 1, 2000. Applicants respectfully request clarification on this matter in the next Official Action.

With respect to section 22 of the outstanding Official Action, the Official Action urges that claim 22 is rejected under 35 U.S.C. §103(a) as being unpatentable over the Valle reference in view of Arntzen *et al.* (US Pat. No. 6,194,560). Applicants respectfully traverse this rejection because the Valle reference does not qualify as prior art under 35 U.S.C. §103(a).


As acknowledged at section 6 of the Official Action dated September 23, 2004, "the instant application is a national stage 371 application of PCT/EP99/03509, filed May 21, 1999 and claims foreign priority to the application, 9801852-6, filed May 26, 1998". Thus, the instant application has a priority date that is prior to the publication date of the Valle reference. Accordingly, Applicants respectfully submit that the Valle reference does not qualify as prior art under 35 U.S.C. §103(a), and the rejection set forth in section 22 of the outstanding Official Action should therefore be withdrawn.

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In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,

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